PAIN

Pain 79 (1999) 105–111

Review Article

# The cortical representation of pain

Rolf-Detlef Treede[a,*], Daniel R. Kenshalo[b], Richard H. Gracely[b], Anthony K.P. Jones[c]

[a] *Johannes-Gutenberg-University, Saarstr. 21, D-55099 Mainz, Germany*
[b] *National Institute of Dental Research, Bethesda, MD, USA*
[c] *Rheumatic Diseases Centre, Hope Hospital, Salford, Manchester, UK*

Received 22 June 1998; accepted 31 August 1998

**Abstract**

Anatomical and physiological studies in animals, as well as functional imaging studies in humans have shown that multiple cortical areas are activated by painful stimuli. The view that pain is perceived only as a result of thalamic processing has, therefore, been abandoned, and has been replaced by the question of what functions can be assigned to individual cortical areas. The following cortical areas have been shown to be involved in the processing of painful stimuli: primary somatosensory cortex, secondary somatosensory cortex and its vicinity in the parietal operculum, insula, anterior cingulate cortex and prefrontal cortex. These areas probably process different aspects of pain in parallel. Previous psychophysical research has emphasized the importance of separating pain experience into sensory-discriminative and affective-motivational components. The sensory-discriminative component of pain can be considered a sensory modality similar to vision or olfaction; it becomes more and more evident that it is subserved by its own apparatus up to the cortical level. The affective-motivational component is close to what may be considered 'suffering from pain'; it is clearly related to aspects of emotion, arousal and the programming of behaviour. This dichotomy, however, has turned out to be too simple to explain the functional significance of nociceptive cortical networks. Recent progress in imaging technology has, therefore, provided a new impetus to study the multiple dimensions of pain. 

*Keywords:* Nociceptive pathways; Somatosensory cortex; Limbic system; Multidimensional pain experience; Imaging

## 1. Introduction

For many years it has been a matter of debate whether the cerebral cortex is involved in pain perception at all. The idea that pain is perceived in the thalamus dates back to the report by Head and Holmes (1911), which was based on careful observations in 16 patients with cortical lesions and 24 patients with thalamic lesions. Other authors have presented evidence for impairment of pain sensation following cortical lesions (Marshall, 1951), but analgesia is not a prominent symptom of such lesions (for review see Kenshalo and Willis, 1991). On the other hand, even surgical interruption of the spinothalamic tract does not abolish pain sensation completely (Lahuerta et al., 1994).

Single cell recordings in the monkey established many years ago, that nociceptive pathways in the somatosensory system project to area 3b and 1 of the primary somatosensory cortex (Kenshalo and Isensee, 1983), as well as to the secondary somatosensory cortex and neighbouring posterior parietal cortex (Dong et al., 1989). Why then, has the involvement of the cerebral cortex in pain sensation been denied for such a long time? This may be partly due to an overemphasis on the suffering component that is part of the pain experience. The definition of pain developed by the IASP, however, clearly indicates that pain has a sensory component in addition to its strong emotional component:

* Corresponding author. Tel.: +49-6131-395715; fax: +49-6131-395902; e-mail: treede@mail.uni-mainz.de

0304-3959/99/$ - see front matter 
PII: S0304-3959(98)00184-5

> Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage, (Merskey, 1986).

Any conceptual framework of the cortical representation of pain has to take into account its multiple dimensions, such as the sensory-discriminative, affective-motivational, and cognitive-evaluative components of pain (Melzack and Casey, 1968). The sensory-discriminative component of pain has been ascribed to the lateral nociceptive system, which projects through specific lateral thalamic nuclei. This part of the nociceptive system has been studied extensively, and evidence has accumulated that its cellular properties (from primary afferents to the somatosensory cortex) can fully account for the sensory-discriminative capacity of pain perception. The central processing of the affective-motivational component of pain in the medial nociceptive system (named after its projection through medial thalamic nuclei) is less clear, possibly in part because it involves intralaminar thalamic nuclei which are known to provide non-specific input to large parts of the cerebral cortex. Likewise, there does not seem to be much progress in our understanding of the neurobiological basis of the cognitive-evaluative component of pain.

Since positron emission tomography (PET) was first used to study functional activation in the human brain by acute heat pain (Jones et al., 1991; Talbot et al., 1991), the cortical representation of pain has become one of the most active areas in pain research. Both studies agreed in that a part of the anterior cingulate cortex was activated (a projection target of the medial nociceptive system), but disagreed on the activation of the somatosensory cortex (a projection target of the lateral nociceptive system). These and several subsequent studies have demonstrated that the medial nociceptive system also involves parts of the cerebral cortex. As a consequence, the participation of the cerebral cortex in pain perception is no longer seriously doubted, and the emphasis in current dispute has shifted towards the question of what specific functions the cortical areas subserve in pain perception. It appears likely that sensory, affective and other dimensions of pain are processed in parallel by different parts of the nociceptive system.

In this topical review we intend to discuss the cortical representation of pain from several different viewpoints, including anatomical and physiological approaches in animals, as well as human data. Complete presentation of the literature is beyond the scope of this paper. Readers interested in more detail may consult recent reviews on anatomical and physiological data (Kenshalo and Willis, 1991; Kenshalo and Douglass, 1995), human electrophysiological data (Chen, 1993; Bromm and Desmedt, 1995), and functional imaging studies (Coghill et al., 1994; Apkarian, 1995; Hsieh et al., 1995; Vogt et al., 1996; Casey and Minoshima, 1997; Derbyshire et al., 1997). This topical review was inspired by discussions during a topical workshop at the 8th World Congress on Pain in Vancouver (Treede et al., 1996).

## 2. Cortical areas that receive information from the spinothalamic tract

One way of identifying cortical areas with potentially nociceptive function is to follow the projection pathways originating in the nociceptive areas of the spinal cord dorsal horn (lamina I and V). This way, several nuclei in the lateral thalamus (VPL, VPM, VPI, VMpo) and in the medial thalamus (CL, MDvc, Pf) have been identified, which in turn project to the cortical areas shown in Fig. 1. The distinction of a lateral and medial nociceptive system is thus projected also to the cortical level, with primary and secondary somatosensory cortex (SI and SII) belonging to the lateral and anterior cingulate cortex to the medial system. The insula takes up an intermediate position since it receives its major input from the lateral system, but itself projects to the limbic system. Within the thalamic nuclei listed in Fig. 1, there are groups of neurons that exclusively receive nociceptive input. Since these cell groups are surrounded by neurons with other properties, anatomical data on the cortical projection of entire thalamic nuclei often do not allow to distinguish between nociceptive and non-nociceptive projections. For the primary and secondary somatosensory cortex the specifically nociceptive projection pathways have been determined by identifying thalamocortical projection neurons within these nuclei that are in close contact with

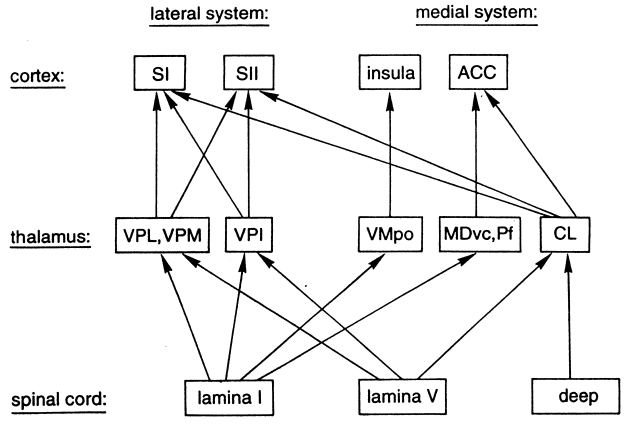


Fig. 1. Cortical areas that receive information from the spinothalamic tract. Main spinothalamic and thalamocortical projections were summarized and simplified from several reports on the central nociceptive pathways in the monkey (Vogt et al., 1979; Willis, 1985; Apkarian and Shi, 1994; Craig, 1996). Cortico-cortical connections are not shown. ACC, anterior cingulate cortex; CL, centrolateral nucleus; MDvc, ventrocaudal part of medial dorsal nucleus; Pf, parafascicular nucleus, SI, primary somatosensory cortex; SII, secondary somatosensory cortex; VMpo, posterior part of ventromedial nucleus; VPI, ventral posterior inferior nucleus; VPL, ventral posterior lateral nucleus; VPM, ventral posterior medial nucleus.

synaptic endings of spinothalamic tract axons (e.g. Apkarian and Shi, 1994); the proportion of nociceptive input is less clear for the pathways leading to the insula and the anterior cingulate cortex. Parts of the prefrontal cortex are also implied in nociceptive processing (Jones and Derbyshire, 1996). In rat, the ventrolateral orbital cortex receives projections from the nucleus submedius of the thalamus, which is a projection target of the spinothalamic tract (for review see Kenshalo and Douglass, 1995). The equivalent nucleus in the primate thalamus, however, has not been identified unequivocally. Prefrontal, as well as other cortical areas may receive nociceptive input via cortico-cortical connections; these connections, however, are difficult to trace because no cortical area has been identified that exclusively processes nociceptive input and could thus be the starting point for an anatomical tracer study.

Physiological studies use functional criteria that are independent of whether the projection is direct or indirect, to identify cortical areas that receive information from the spinothalamic tract. These functional criteria consist of the identification of properties that are known to be specific for primary nociceptive afferents (high threshold, intensity coding in the noxious range, polymodality, sensitization following injury as a correlate of primary hyperalgesia) or second-order nociceptive neurons in the spinal cord (receptive field changes following injury as a correlate of secondary hyperalgesia). Only three cortical regions have been studied in some detail with single cell recordings: primary somatosensory cortex (e.g. Kenshalo and Isensee, 1983; Lamour et al., 1983), secondary somatosensory cortex (Robinson and Burton, 1980; Dong et al., 1989), and anterior cingulate cortex (Sikes and Vogt, 1992; Yamamura et al., 1996). All three areas contain both nociceptive specific neurons that only respond to noxious stimuli and wide-dynamic-range neurons that have convergent input from nociceptive and other afferents.

Nociceptive neurons in the primary somatosensory cortex are arranged in clusters that do not occupy all layers within a cortical column but seem to be confined to the deeper layers III–V (for review see Kenshalo and Douglass, 1995). These neurons have small receptive fields that are arranged in a somatotopic pattern along the post-central gyrus (Lamour et al., 1983). They encode graded stimulus intensities and their response properties change after injury consistent with both primary and secondary hyperalgesia. These neurons are well suited to subserve sensory-discriminative aspects of pain.

Although the secondary somatosensory cortex receives appropriate spinothalamic projections, evidence from single cell recordings for nociceptive neurons along the upper bank of the lateral sulcus is mixed. Some nociceptive neurons with large receptive fields have been described in the caudal part of SII (Whitsel et al., 1969) and in neighbouring areas 7b and retroinsular cortex (Robinson and Burton, 1980), but the core of SII appears to contain few nociceptive neurons. In the border region between area 7b and SII, some neurons that responded exclusively to noxious mechanical stimulation have been found to accurately encode stimulus duration (Dong et al., 1989). In the same region, about half of the heat-sensitive nociceptive neurons encoded intensity of noxious heat stimulation (Dong et al., 1994). In general, however, encoding of stimulus intensity was found to be poor. For these reasons, SII and its vicinity do not seem to play a prominent role in the sensory-discriminative component of pain. Task-related responses and convergence with visual input (for threatening stimuli approaching the nociceptive receptive field) instead suggest a role in spatially directed attention towards noxious stimuli (Dong et al., 1994; Kenshalo and Douglass, 1995).

Nociceptive neurons in the anterior cingulate cortex have large receptive fields that may encompass the whole body surface and they exhibit some intensity coding for noxious mechanical stimuli (Sikes and Vogt, 1992; Yamamura et al., 1996). The receptive field properties of these cortical neurons are similar to those of the medial thalamic nuclei and the spinal neurons that project to these nuclei (Willis, 1985). The anterior cingulate cortex is thought to play a role in affective-motivational pain processing because it is part of the limbic system and has efferent connections to other limbic, motor and autonomic nervous system areas. There is no positive evidence for this function from single cell recordings; rather, the neuronal properties were found not to be suitable for sensory-discriminative coding.

Another cortical area that projects to the limbic system and receives nociceptive input is the insula. The somatosensory region within the insula comprises parts of the posterior (granular) and anterior (dysgranular) areas; it is part of a sensory-limbic projection pathway from SII to the amygdala, and is considered to be involved in tactile object recognition and tactile learning (Friedman et al., 1986). Nociceptive input from the spinothalamic tract has been suggested to reach anterior parts of the insula directly via the thalamic relay nucleus VMpo (Craig et al., 1994). The insula is also considered a visceral sensory and visceral motor area (for review see Augustine, 1996), and may thus serve a sensory integrative function for pain, taste and other visceral sensations, as well as tactile and vestibular input. Due to its projection to the amygdala, the insula may also be involved in affective and emotional processes.

## 3. The sensory-discriminative component of pain

The sensory-discriminative component of pain encompasses at least three aspects: stimulus localization, intensity discrimination and quality discrimination. The human capacity to perceive the location of tissue injury is used daily in medical practice, when doctors ask the question ‘where does it hurt?’. Localization of noxious stimuli is precise for the skin, more difficult for deep tissue such as joints and muscles, and notoriously poor for the viscera (for recent experimental data see Arendt-Nielsen, 1997). Stimulus localization has traditionally been ascribed to simultaneous

activation of the 'lemniscal' pathways. This notion is based on the unfair comparison of tactile acuity at the finger tips and referred pain from viscera. Tactile acuity outside the 'foveal' area of the finger tips and lips, however, is much less than commonly appreciated. On the human hand, for example, the mean localization error for tactile stimuli was 12 ± 2 mm; localization of laser radiant heat stimuli in the same skin area was almost equal with a mean error of 14 ± 3 mm (Moore and Schady, 1995). Cutaneous localization of Aδ-fiber mediated pricking pain is very good, and is mediated by nociceptive afferents, because these radiant heat pulses do not activate mechanoreceptors (Bromm et al., 1984). Similar values were reported for burning pain (Moore and Schady, 1995), suggesting that even C-fiber mediated pain is well localized. This result sharply contradicts a widely accepted view, but has been supported by a study that demonstrated mean localization errors of about 10 mm for heat stimuli, mustard oil and histamine, during an A-fiber block by nerve compression (Koltzenburg et al., 1993).

These psychophysical findings demonstrate that the nociceptive system in humans provides sufficient spatial information to account for our capacity to know 'where it hurts'. What is the neural basis for this capacity? Receptive fields of nociceptive neurons show somatotopic organization in the dorsal horn (Woolf and Fitzgerald, 1986), lateral thalamus (Albe-Fessard et al., 1985; Lenz et al., 1994) and the primary somatosensory cortex (Lamour et al., 1983; Kenshalo and Willis, 1991). Receptive field sizes in SI are smaller than in the spinal cord and thalamus, possibly due to lateral inhibition, and match the pain localization capacity. Thus, all existing evidence favours the view that SI is involved in stimulus localization for the nociceptive system, as well as the tactile system (this does not imply that the body scheme actually resides in SI, neither for pain nor for touch). Indirect evidence for this concept is provided by PET studies in humans: those studies that used heat stimuli at several spots demonstrated increased perfusion of SI (Talbot et al., 1991; Casey et al., 1994; Coghill et al., 1994), whereas studies with fixed stimulus location did not (Jones et al., 1991; Derbyshire et al., 1994). This may be interpreted to indicate that only tasks with a stimulus localization component activate SI. This hypothesis, however, has not yet been proved explicitly in a prospective study.

The capacity to encode different intensities of noxious stimuli is one of the criteria to identify nociceptive neurons (Dubner et al., 1977; Willis, 1985). Several authors have proposed that WDR neurons encode stimulus intensities better than nociceptive specific neurons (e.g. Maixner et al., 1986). Since WDR neurons often have large receptive fields, this could indicate that stimulus localization and intensity discrimination are subserved by two different channels of the nociceptive system. This concept was supported by a recent case report on a patient with a lateral thalamic lesion, who showed very poor pain spatial localization, but only marginally altered pain intensity discrimination (Greenspan et al., 1997). Intensity coding has been demonstrated for nociceptive neurons in SI and to a certain extent also in SII. Intensity coding is a poor criterion to identify neurons involved in sensory-discriminative aspects of pain, since the affective-motivational component of pain also depends on stimulus intensity. In a study that demonstrated different relative unpleasantness of four experimental painful stimuli, perceived intensity and unpleasantness both were nevertheless related to stimulus intensity (Rainville et al., 1992). Likewise, neurons in medial thalamic nuclei of primates (CL, CM, Pf, LD, MD) and in anterior cingulate cortex of the rabbit have been shown to encode the intensity of noxious heat stimuli (Bushnell and Duncan, 1989; Sikes and Vogt, 1992).

Current evidence supports the traditional view that the lateral nociceptive system subserves the sensory-discriminative component of pain. Different aspects of this pain component (detection, localization, intensity discrimination, quality) may be processed in parallel by separate pathways. In contrast to traditional views, there is no evidence that the lemniscal system participates in any of these functions. Thus, nociception is established as a sensory modality within the somatosensory system.

## 4. The affective-motivational component of pain

The IASP definition of pain puts a major emphasis on the unpleasantness of the experience mediated by the nociceptive system (Merskey, 1986). Thus, the affective-motivational component is an essential part of pain sensation. This component encompasses several aspects that are closely related: the negative hedonic quality and emotional reactions ('I don't like it'), a general activation or arousal and stimulus-related selective attention, and the drive to terminate the stimulus causing this sensation ('stop it'). Some of these functions can be considered second-order sensory processing, whereas the latter is a premotor function. The affective-motivational component of pain is classically associated with the medial nociceptive system, which in turn is connected to the limbic system.

One part of the medial nociceptive system, the anterior cingulate cortex, has recently become the focus of attention, as virtually all PET studies of acute pain stimuli gave evidence of activation in that area (for review see Casey and Minoshima, 1997), including one study where pain was elicited as an illusion by combination of non-noxious stimuli (Craig et al., 1996). Each of the three dipole source analyses of pain related evoked potentials also yielded a dipole in this area (Tarkka and Treede, 1993; Bromm and Chen, 1995; Valeriani et al., 1996). The anterior cingulate cortex is a functionally heterogeneous brain area that has been implicated in the integration of affect, cognition and response selection in addition to aspects of social behaviour (for review see Devinsky et al., 1995). Passive functions

(emotion, attention) are represented more frontally, whereas a premotor part of the anterior cingulate cortex is situated more posteriorly below the supplementary motor area (Picard and Strick, 1996). The centre of the area activated by acute painful stimuli was either between these locations (e.g. Hsieh et al., 1995), or consisted of a posterior site in the mid-cingulate cortex and an anterior site in the perigenual cingulate cortex (Vogt et al., 1996). It is still debated, whether the anterior cingulate cortex contains a specific nociceptive area, or whether painful stimuli non-specifically recruit several cingulate areas, such as the mid-cingulate executive (premotor) area and perigenual areas that may be more concerned with affective processing and autonomic responses.

Activation of the anterior cingulate cortex apparently was independent of explicit motor tasks in the PET studies, because subjects were instructed to give ratings of perceived intensity only after the scan (Jones et al., 1991; Talbot et al., 1991; Casey et al., 1994; Coghill et al., 1994). It has been argued that lying quietly inside a PET scanner while experiencing painful stimuli requires active suppression of motor commands for withdrawal. This hypothesis is open to experimental verification by varying the motor component of the tasks used. Moreover, it may be useful to perform psychophysical studies that quantify the motivational component for different painful stimuli. To pinpoint the cortical representation of the motivational component of pain, future imaging studies may then use painful stimuli that are matched for subjective intensity, but differ with respect to their drive to withdraw.

Activation of the anterior cingulate cortex is often interpreted to represent the affective (suffering) component of pain. Two caveats apply: (1) brief experimental pain stimuli evoke less of an affective response than clinical pain or some tonic pain models such as the cold pressor test (Chen and Treede, 1985) (2) the painful stimulus used in the PET studies (noxious heat) evokes an even lower affective response than, e.g. electrically-evoked or ischemic pain (Rainville et al., 1992). To pinpoint the representation of the affective component of pain, subtraction studies are needed with two painful stimuli that are matched for subjective intensity but differ as to unpleasantness. A recent study on selective manipulation of unpleasantness by hypnosis is a first step in this direction (Rainville et al., 1997).

Table 1

Putative functional roles of cortical areas that are activated by noxious stimuli

| Cortical area | Possible functions |
|---|---|
| SI | Sensory discriminative in general, alternatively: stimulus localization |
| SII and 7b | Sensory integrative (touch, pain, visual), spatially directed attention |
| Insula | Sensory integrative (touch, pain, taste, vestibular), visceral sensory, visceral motor, limbic integration |
| Anterior cingulate | Response selection, motor suppression, attention, affect |
| Prefrontal cortex | Affect, emotion, memory |

Table 2

Components of a task involving painful stimuli

| Component | Examples |
|---|---|
| Sensory discriminative | Discrimination of stimulus location, intensity, quality |
| Sensory integrative | Integration of tactile, nociceptive and other input |
| Affective motivational | Hedonic quality, arousal, response selection |
| Motor | Planning and execution of motor programs |
| Situation specific | Claustrophobia inside MRI scanner |

The affective-motivational component of pain may also be processed in the insula. Contralateral insula was the second most frequently activated area in the human PET studies of acute pain, only surpassed by the anterior cingulate cortex (Casey and Minoshima, 1997). The insula projects to parts of the amygdala (Augustine, 1996), a part of the limbic system that is traditionally associated with emotions. Due to their close proximity, insula and SII are difficult to separate in imaging studies in humans.

## 5. Conclusions and outlook

The cortical representation of pain has become an important matter of current debate due to recent imaging studies. In spite of some controversies about details the degree of consistency across these studies is remarkable, and the list of cortical areas that are supposed to subserve nociceptive functions is relatively short (Table 1). For most of these areas, however, more than one putative function has been proposed. By looking at small differences in experimental paradigms between studies, a retrospective analysis may lead the way how to differentiate between these functions (e.g. stimulus localization as a prerequisite for SI activation). An important task for the future is to perform controlled prospective studies to test these hypotheses. In addition to PET, which is available only at a limited number of centres, other imaging techniques such as single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) can be used to address the same problems. By employing modern source analysis techniques, electro- and magneto-encephalographic (EEG and MEG) studies will also be able to contribute to solve the puzzle of cortical representation of pain. All of these studies face the problem that even psychophysical tasks using controlled experimental painful stimuli have many components (Table 2) that will activate several different brain areas. Clinical pain states in addition reflect plastic changes of the central nervous system, and were therefore deliberately not discussed in this topical review.

What is needed most in the near future, therefore, is not

an improvement in imaging techniques, but rather the development of new experimental paradigms that separate different aspects of pain more clearly than currently possible. This way, the recent PET studies have brought us back to the roots of the IASP, i.e. to the definition of pain and its components (cf. Melzack and Casey, 1968). Instead of providing a final answer about the cortical representation of pain, these studies have raised new questions for psychophysical research on the multiple dimensions of pain, especially its affective-motivational and cognitive-evaluative constituents.

## Acknowledgements

The authors appreciate many spirited discussions with A.D. Craig and R.C. Coghill.

## References

Albe-Fessard, D., Berkley, K.J., Kruger, L., Ralston, H.J. and Willis, W.D., Diencephalic mechanisms of pain sensation, Brain Res. Rev., 9 (1985) 217–296.

Apkarian, A.V., Functional imaging of pain: New insights regarding the role of the cerebral cortex in human pain perception, Semin. Neurosci., 7 (1995) 279–293.

Apkarian, A.V. and Shi, T., Squirrel monkey lateral thalamus. I. Somatic nociresponsive neurons and their relation to spinothalamic terminals, J. Neurosci., 14 (1994) 6779–6795.

Arendt-Nielsen, L., Induction and assessment of experimental pain from human skin, muscle and viscera. In: T.S. Jensen, J.A. Turner and Z. Wiesenfeld-Hallin (Eds.), Proceedings of the 8th World Congress on Pain, Progress in Pain Research and Management Vol. 8, IASP Press, Seattle, WA, 1997, pp. 393–425.

Augustine, J.R., Circuitry and functional aspects of the insular lobe in primates including humans, Brain Res. Rev., 22 (1996) 229–244.

Bromm, B. and Chen, A.C.N., Brain electrical source analysis of laser evoked potentials in response to painful trigeminal nerve stimulation, Electroenceph. clin. Neurophysiol., 95 (1995) 14–26.

Bromm, B. and Desmedt, J.E., Pain and the Brain: From Nociception to Cognition, Raven Press, New York, 1995.

Bromm, B., Jahnke, M.T. and Treede, R.-D., Responses of human cutaneous afferents to $CO_2$ laser stimuli causing pain, Exp. Brain Res., 55 (1984) 158–166.

Bushnell, M.C. and Duncan, G.H., Sensory and affective aspects of pain perception: is medial thalamus restricted to emotional issues?, Exp. Brain Res., 78 (1989) 415–418.

Casey, K.L. and Minoshima, S., Can pain be imaged? In: T.S. Jensen, J.A. Turner and Z. Wiesenfeld-Hallin (Eds.), Proceedings of the 8th World Congress on Pain, Progress in Pain Research and Management Vol. 8, IASP Press, Seattle, WA, 1997, pp. 855–866.

Casey, K.L., Minoshima, S., Berger, K.L., Koeppe, R.A., Morrow, T.J. and Frey, K.A., Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli, J. Neurophysiol., 71 (1994) 802–807.

Chen, A.C.N., Human brain measures of clinical pain – a review.1. topographic mappings, Pain, 54 (1993) 115–132.

Chen, A.C.N. and Treede, R.-D., The McGill pain questionnaire in the assessment of phasic and tonic experimental pain: behavioral evaluation of the 'pain inhibiting pain' effect, Pain, 22 (1985) 67–69.

Coghill, R.C., Talbot, J.D., Evans, A.C., Meyer, E., Gjedde, A., Bushnell, M.C. and Duncan, G.H., Distributed processing of pain and vibration by the human brain, J. Neurosci., 14 (1994) 4095–4108.

Craig, A.D., An ascending general homeostatic afferent pathway originating in lamina I, Prog. Brain Res., 107 (1996) 225–242.

Craig, A.D., Bushnell, M.C., Zhang, E.T. and Blomqvist, A., A thalamic nucleus specific for pain and temperature sensation, Nature, 372 (1994) 770–773.

Craig, A.D., Reiman, E.M., Evans, A. and Bushnell, M.C., Functional imaging of an illusion of pain, Nature, 384 (1996) 258–260.

Derbyshire, S.W.G., Jones, A.K.P., Devani, P., Friston, K.J., Feinmann, C., Harris, M., Pearce, S., Watson, J.D.G. and Frackowiak, R.S.J., Cerebral responses to pain in patients with atypical facial pain measured by positron emission tomography, J. Neurol. Neurosurg. Psychiatry, 57 (1994) 1166–1172.

Derbyshire, S.W.G., Jones, A.K.P., Gyulai, F., Clark, S., Townsend, D. and Firestone, L.L., Pain processing during three levels of noxious stimulation produces differential patterns of central activity, Pain, 73 (1997) 431–445.

Devinsky, O., Morrell, M.J. and Vogt, B.A., Contributions of anterior cingulate cortex to behaviour, Brain, 118 (1995) 279–306.

Dong, W.K., Salonen, L.D., Kawakami, Y., Shiwaku, T., Kaukoranta, E.M. and Martin, R.F., Nociceptive responses of trigeminal neurons in SII-7b cortex of awake monkeys, Brain Res., 484 (1989) 314–324.

Dong, W.K., Chudler, E.H., Sugiyama, K., Roberts, V.J. and Hayashi, T., Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys, J. Neurophysiol., 72 (1994) 542–564.

Dubner, R., Price, D.D., Beitel, R.E. and Hu, J.W., Peripheral neural correlates of behavior in monkey and human related to sensory-discriminative aspects of pain. In: D.J. Anderson and B. Matthews (Eds.), Pain in the Trigeminal Region. Elsevier, Amsterdam, 1977, pp. 57–66.

Friedman, D.P., Murray, E.A., O'Neill, J.B. and Mishkin, M., Cortical connections of the somatosensory fields of the lateral sulcus of macaques: evidence for a corticolimbic pathway for touch, J. Comp. Neurol., 252 (1986) 323–347.

Greenspan, J.D., Joy, S.E., McGillis, S.L.B., Checkosky, C.M. and Bolanowski, S.J., A longitudinal study of somesthetic perceptual disorders in an individual with a unilateral thalamic lesion, Pain, 72 (1997) 13–25.

Head, H. and Holmes, G., Sensory disturbances from cerebral lesions, Brain, 34 (1911) 102–254.

Hsieh, J.C., Belfrage, M., Stoneelander, S., Hansson, P. and Ingvar, M., Central representation of chronic ongoing neuropathic pain studied by positron emission tomography, Pain, 63 (1995) 225–236.

Jones, A.K.P., Brown, W.D., Friston, K.J., Qi, L.Y. and Frackowiak, R.S.J., Cortical and subcortical localization of response to pain in man using positron emission tomography, Proc. R. Soc. Lond. B, 244 (1991) 39–44.

Jones, A.K.P. and Derbyshire, S.W.G., Cerebral mechanisms operating in the presence and absence of inflammatory pain, Ann. Rheum. Dis., 55 (1996) 411–420.

Kenshalo, D.R. and Isensee, O., Responses of primate SI cortical neurons to noxious stimuli, J. Neurophysiol., 50 (1983) 1479–1496.

Kenshalo, D.R. and Douglass, D.K., The role of the cerebral cortex in the experience of pain. In: B. Bromm and J.E. Desmedt (Eds.), Pain and the Brain: From Nociception to Cognition, Raven Press, New York, 1995, pp. 21–34.

Kenshalo, D.R. and Willis, W.D., The role of the cerebral cortex in pain sensation. In: A. Peters (Eds.), Cerebral Cortex, Vol. 9, Plenum Press, New York, 1991, pp. 153–212.

Koltzenburg, M., Handwerker, H.O. and Torebjörk, H.E., The ability of humans to localise noxious stimuli, Neurosci. Lett., 150 (1993) 219–222.

Lahuerta, J., Bowsher, D., Lipton, S. and Buxton, P.H., Percutaneous cervical cordotomy: a review of 181 operations on 146 patients with a study on the location of 'pain fibers' in the C-2 spinal cord segment of 29 cases, J. Neurosurg., 80 (1994) 975–985.

Lamour, Y., Willer, J.C. and Guilbaud, G., Rat somatosensory (SmI) cortex: I. Characteristics of neuronal responses to noxious stimulation and comparison with responses to non-noxious stimulation, Exp. Brain Res., 49 (1983) 35–45.

Lenz, F.A., Kwan, H.C., Martin, R., Tasker, R., Richardson, R.T. and Dostrovsky, J.O., Characteristics of somatotopic organization and spontaneous neuronal activity in the region of the thalamic principal sensory nucleus in patients with spinal cord transection, J. Neurophysiol., 72 (1994) 1570–1587.

Maixner, W., Dubner, R., Bushnell, M.C., Kenshalo, D.R. and Oliveras, J.-L., Wide-dynamic-range dorsal horn neurons participate in the encoding process by which monkeys perceive the intensity of noxious heat stimuli, Brain Res., 374 (1986) 385–388.

Marshall, J., Sensory disturbances in cortical wounds with special reference to pain, J. Neurol. Neurosurg. Psychiatry, 14 (1951) 187–204.

Melzack, R. and Casey, K.L., Sensory, motivational, and central control determinants of pain. A new conceptual model. In: D.R. Kenshalo (Eds.), The Skin Senses. Charles C. Thomas, Springfield, IL, 1968, pp. 423–443.

Merskey, H., Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms, Pain Suppl., 3 (1986) S1–S225.

Moore, C.E.G. and Schady, W., Cutaneous localisation of laser induced pain in humans, Neurosci. Lett., 193 (1995) 208–210.

Picard, N. and Strick, P.L., Motor areas of the medial wall: a review of their location and functional activation, Cereb. Cortex, 6 (1996) 342–353.

Rainville, P., Duncan, G.H., Price, D.D., Carrier, B. and Bushnell, M.C., Pain affect encoded in human anterior cingulate but not somatosensory cortex, Science, 277 (1997) 968–971.

Rainville, P., Feine, J.S., Bushnell, M.C. and Duncan, G.H., A psychophysical comparison of sensory and affective responses to four modalities of experimental pain, Somatosens. Motor Res., 9 (1992) 265–277.

Robinson, C.J. and Burton, H., Somatic submodality distribution within the second somatosensory (SII), 7b, retroinsular, postauditory and granular insular cortical areas of *M. fascicularis*, J. Comp. Neurol., 192 (1980) 93–108.

Sikes, R.W. and Vogt, B.A., Nociceptive neurons in area 24 of rabbit cingulate cortex, J. Neurophysiol., 68 (1992) 1720–1732.

Talbot, J.D., Marrett, S., Evans, A.C., Meyer, E., Bushnell, M.C. and Duncan, G.H., Multiple representations of pain in human cerebral cortex, Science, 251 (1991) 1355–1358.

Tarkka, I.M. and Treede, R.-D., Equivalent electrical source analysis of pain-related somatosensory evoked potentials elicited by a $CO_2$ laser, J. Clin. Neurophysiol., 10 (1993) 513–519.

Treede, R.-D., Craig, A.D., Kenshalo, D.R., Coghill, R.C. and Jones, A.K.P., Cortical representation of pain, Abstracts: 8th World Congress on Pain, (1996) p. 104.

Valeriani, M., Rambaud, L. and Mauguière, F., Scalp topography and dipolar source modelling of potentials evoked by $CO_2$ laser stimulation of the hand, Electroenceph. clin. Neurophysiol., 100 (1996) 343–353.

Vogt, B.A., Derbyshire, S. and Jones, A.K.P., Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging, Eur. J. Neurosci., 8 (1996) 1461–1473.

Vogt, B.A., Rosene, D.L. and Pandya, D.N., Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey, Science, 204 (1979) 205–207.

Whitsel, B.L., Petrucelli, L.M. and Werner, G., Symmetry and connectivity in the map of the body surface in somatosensory area II of primates, J. Neurophysiol., 32 (1969) 170–183.

Willis, W.D., The Pain System, Karger, Basel, 1985.

Woolf, C.J. and Fitzgerald, M., Somatotopic organization of cutaneous afferent terminals and dorsal horn neuronal receptive fields in the superficial and deep laminae of the rat lumbar spinal cord, J. Comp. Neurol., 251 (1986) 517–531.

Yamamura, H., Iwata, K., Tsuboi, Y., Toda, K., Kitajima, K., Shimizu, N., Nomura, H., Hibiya, J., Fujita, S. and Sumino, R., Morphological and electrophysiological properties of ACCx nociceptive neurons in rats, Brain Res., 735 (1996) 83–92.